REMARKS

Rejection under 35 USC 102:

Claim 1 is rejected under §102 as being anticipated by US 5,698,531. The Action states that the '531 patent teaches a process for delivering a polynucleotide into an extravascular parenchymal cell of a mammal. Applicants respectfully disagree.

It is well know in the art that arteries are composed of 3 layers or tunics: the intima, the media, and the adventitia. The innermost tunica intima is composed of endothelial cells. The middle layer, the tunic media, is composed of smooth muscle cells. The outer connective layer is the tunica adventitia. Larger vessels have much more smooth muscle and an elastic lamina (membrane) just under the endothelium. In very large arteries an external elastic membrane may be present between the media and collagen-rich adventitia. All of these layers are considered to be part of the blood vessel by a person having knowledge in the art.

Therefore, the interpretation of the Nabel (1995) statement, "delivery of DNA transmurally and gene expression in the media," to mean "cells beyond the blood vessel" is not a reasonable interpretation. Furthermore, the Nabel method is principally concerned with delivery to endothelial and smooth muscle cells, i.e. the tunica intima and tunica media. In blood vessels, the tunica intima forms a barrier that prevents interaction of components in the lumen of the vessel from interaction with smooth muscle cells of the tunica media, hence the intentional injury to the endothelial lining in the method taught by Nabel. Delivery to the media, as an indication of the extent of delivery, fails to reach even the outermost layer of the vessel itself and thus cannot be reasonably interpreted to mean delivery to extravascular cells.

As further indication that the method taught by Nabel fails to achieve delivery to extravascular parenchymal cells, Applicants draw attention to statements made by E. Nabel in an amendment filed on Nov. 22, 1993 in the file history of US Patent No. 5,698,531. On page 5 of the amendment, Nabel states "Site-specific instillation of the various genes is achieved by... introducing the DNA or RNA sequences via a balloon catheter which isolates these sequences to a specific region of the arterial wall... By transforming the cells in the blood artery, expressed therapeutic gene products are steadily profused downstream into the involved tissue. The invention relies on recombinant gene expression within transduced vascular cells in a localized arterial segment... ." On page 12 of the amendment, Nabel states, "These results are significant because they demonstrate that the direct injection of recombinant DNA in vivo results not only in the transformation of the arterial wall at the injection site, but also in expression of the desired gene product..." and "... human patients were treated by direct gene transfer... This gene was expressed in tissues localized to the instillation site... ." These statements clearly indicate that the transformed cells are restricted not only to cells of the arterial wall, but to cells of a very localized section of the arterial wall--a section delimited by the balloon catheters.

In addition, as indicated, the method taught by Nabel provides for delivery of a therapeutic protein to a downstream tissue only by expression and secretion of the protein from upstream arterial cells. The method taught by Nabel provides no direction on delivery to cells other than

endothelial and smooth muscle cells located in a very small, defined region of a blood vessel. DNA is not directly delivered to parenchymal cells. Applicants recognize that general background statements made in Nabel '531 suggest that DNA may be delivered to parenchymal cells using the described method. However, no evidence of such delivery is provided, either in '531 or in subsequent publications authored by the inventor. Nor is there any specific teaching of a method in which an extravascular cell is the intended delivery target.

The invention taught by the Applicants provides a significantly improved nucleic acid delivery procedure in which nucleic acid can be delivered to extravascular cells directly, the cells need not be located in the immediate vicinity of the instillation point, and the process is not limited to delivery of nucleic acid encoding secreted proteins in order to achieve a therapeutic effect on extravascular parenchymal cells.

Examiner argues that because Nabel does not specifically state that extravascular cells are not targeted, the method of Nabel teaches delivery to extravascular cells. Again, this is not a reasonable argument for one skilled in the art. There is a broad jump from "In order to enable delivery to an extravascular cell," at a minimum, delivery to that extravascular cell must in fact be shown.

Rejection under 35 USC 103:

Claims 1-3 are rejected under 35 U.S.C. §103(a) as being unpatentable using US 5,698,531 along with US 2001/0005717. Applicants respectfully disagree and rely on the §102 discussion to over come this §103 rejection.

Applicants believe that they have overcome the rejections in the Office Action. Claim 3 has been amended to be placed in allowable condition.

If the Examiner would like more information or has any questions, please feel free to contact me.

Respectfully submitted,

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I hereby certify that this correspondence is being sent by facsimile transmission to art unit 1636, 703.308.4242; Commissioner for Patents, Washington, DC on 5/12/03.

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